# Alcohol as a Cause of Cancer

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This is a review of the epidemiologic literature on alcohol and risks of various cancers. Alcohol has consistently been related to risks of squamous cell carcinomas of the mouth, oral pharynx, larynx, and esophagus in multiple studies of varying design. The joint effects of alcohol and smoking are greater than additive, and are probably multiplicative, suggesting biological synergism. All major types of alcoholic beverages have been causally implicated in the genesis of these diseases. The influence of alcohol on risks of upper aerodigestive tract cancers may be greater in persons with marginal nutritional status than in better-nourished individuals. Alcohol also has been associated with an increased risk of adenocarcinomas of the esophagus, gastro-esophageal junction, and gastric cardia, but the relationship is not as strong as for squamous cell esophageal carcinomas. Alcohol and tobacco account for over 80% of the squamous carcinomas of the mouth, pharynx, larynx, and esophagus in the United States. Risks of cancers of the distal stomach, pancreas, colon, and rectum have not been consistently related to alcohol, although possible relationships between beer drinking and rectal cancer and between heavy use of alcohol and pancreatic cancer warrant further study. Studies of alcohol and liver cancer, in which the confounding influence of hepatitis B was considered, have yielded inconsistent results and should be replicated. An association between heavy alcohol use and breast cancer has been observed in most studies, even after controlling for known risk factors for breast cancer, and additional investigations of this issue are warranted. — Environ Health Perspect 103(Suppl 8):153–160 (1995)

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## Introduction

This paper reviews and evaluates the evidence from epidemiologic studies for the affect of alcohol on risks of various cancers. Cancers of particular concern are those of the upper aerodigestive tract. Other neoplasms of interest include those of the lower digestive tract, pancreas, liver, and breast.

## Methods

The information summarized in this paper is based on a review of the English language literature. In some instances, secondary sources have been used. These include reviews by responsible expert committees such as those convened by the International Agency for Research on Cancer (IARC) (1) and reviews by individual authors that have been published in peer-reviewed journals. When such reviews are used, they have been updated with reports that have appeared since these reviews were written.

Evidence from three types of epidemiologic investigations has been considered. One type of investigation is the cohort study with external comparisons. In this

type of investigation, incidence or mortality rates in alcoholics or other groups heavily exposed to alcohol are compared with rates in the general population. Such studies are easy to conduct because they are based on data from existing records, are quite common, and often include large numbers of exposed individuals and therefore have considerable power to detect increased risks in relation to alcohol use. However, investigators conducting such studies are rarely able to control for the possible confounding effects of other risk factors for the cancers under study. Also, it usually is not possible to characterize individuals in such studies with respect to the details of their alcohol use.

A second type of cohort study involves use of internal comparisons. In such studies, individuals within a cohort who have been exposed to varying levels of alcohol are compared with respect to their rates of various neoplasms. These studies have several advantages over the cohort studies that use external comparisons in that more detailed information is usually available on the details of alcohol use by the study subjects and information on other risk factors of interest is more frequently available. However, these studies are more difficult to conduct because they involve collection of information directly from the study subjects. Therefore, these types of studies are less common and often are of smaller size than the cohort studies using external comparisons.

The third type of epidemiologic investigation is the case–control study. These

studies provide detailed information on the features of alcohol use and other potential confounding factors and if they include sufficient numbers of cases and controls, have considerable statistical power to assess increased risks in relation to various features of alcohol use as well as possible interactions between alcohol and other risk factors. The major disadvantage of the case–control approach is difficulty in retrospectively assessing study subjects' previous use of alcohol. Of particular concern is differential recall or reporting of alcohol use by cases and controls, which can lead to biased results.

In this paper, results from all three types of investigations have been assembled and the evidence for or against a causal relationship between the neoplasms under consideration and alcohol use has been evaluated, taking into consideration, when possible, relevant biological explanations that have been proposed for observed associations.

## Results

### Oral and Pharyngeal Cancers

The first column of Table 1 summarizes results from cohort studies with external comparisons on neoplasms of the oral cavity and pharynx (1–3). All the studies shown were conducted in areas where nasopharyngeal carcinomas are rare, and it can be assumed that the pharyngeal carcinomas are those that arose from the oral pharynx. An increase in risk of oral and pharyngeal cancers has consistently been observed in these types of studies, which

**Table 1.** Relative risks of oral, laryngeal, and esophageal cancers in cohorts of heavy users of alcohol, external comparisons.

| Study group | Relative risks, 95% CI | | |
| --- | --- | --- | --- |
| | Oral[a] | Larynx | Esophagus |
| Norwegian alcoholics | 4.8 (3.0–7.2) | 3.1 (1.0–7.3) | 4.1 (2.9–5.6) |
| Massachusetts alcoholics | 3.3 (1.8–5.6) | 3.8 (1.4–8.2) | 1.9 (0.4–5.5) |
| U.S. veteran alcoholics | 2.2 (1.1–4.6) | 1.7 (0.7–4.4) | 2.0 (0.9–5.1) |
| Danish brewery workers | 0.8 (0.4–1.5) | 4.3 (1.4–4.9) | 2.1 (1.5–2.8) |
| Canadian alcoholics | 4.2 (2.7–6.3) | 2.0 (1.4–2.7) | 3.2 (1.8–5.2) |
| Danish alcoholics[b] | 1.3 (0.9–1.7) | 3.7 (2.8–4.6) | 5.3 (4.0–6.8) |
| Swedish alcoholics[c] | 4.1 (2.9–5.6) | 3.3 (1.7–6.0) | 6.8 (4.5–9.9) |
| Finnish alcoholics | — | 1.4 (0.3–4.1) | 4.1 (1.4–9.3) |
| Finnish alcohol misusers | — | — | 1.7 (1.4–2.1) |
| Dublin brewery workers | — | — | 0.6 (0.3–1.2) |

[a]Includes both oral cavity and oral pharynx combined. [b]Data from Tonnesen et al. (2). [c]Data from Adami et al. (3).

have included individuals treated for alcoholism and individuals who have been employed in the brewing industry.

Results from cohort studies in which internal comparisons were used are summarized in Table 2 (1,4,5). Again, a consistent increase in risk of oral and pharyngeal cancers has been observed in regular and heavy users of alcohol. Some of these studies showed an increase in risk with increases in the amounts of alcohol consumed.

There have been at least 17 case–control studies of oral and pharyngeal cancers in relation to alcohol use, 10 of which were summarized by an IARC working group in 1988 (1). All of these studies (1,6–12) yielded consistent results, showing an increase in risk with duration of alcohol use or amount of alcohol consumed. In the largest and most comprehensive population-based case–control study, conducted in the United States (13), trends of increasing risk with number of drinks per week were observed in both men and women for cancers of the tongue, elsewhere in the oral cavity, and oral pharynx. The relative risks in relation to any particular level of alcohol consumption were similar for men and women.

Another strong risk factor for oral and pharyngeal cancers is cigarette smoking. The joint effects of smoking and alcohol use on risk of these neoplasms appear to be greater than additive and consistent with a multiplicative effect. This suggests biological synergism, with alcohol probably potentiating the carcinogenic effects of cigarette smoke. However, alcohol appears to be associated with an increase in risk of oral and pharyngeal cancers even in nonsmokers (13).

In studies conducted in North Carolina (14) and Shanghai (15), a relationship of alcohol use to risk was particularly strong in individuals who consumed fresh fruits and vegetables only infrequently. The joint effects of poor nutrition and alcohol use appeared to be more than additive, possibly suggesting biological synergism.

The risks of oral and pharyngeal neoplasms have been associated with consumption of hard liquor, beer, and wine, suggesting that the alcohol in these drinks is the agent responsible for the carcinogenic effect, not impurities or other constituents of these beverages. Reports of associations between oral cancer and use of mouthwash (16) that contains alcohol provide further

evidence that alcohol is the agent in alcoholic beverages responsible for the carcinogenic effect. Also, since mouthwash is not swallowed, this suggests that the mechanism involved is due to some topical effect of ethanol on the oral and pharyngeal mucosa rather than a systemic effect.

Based on data from a large U.S. study (13), Day et al. (17) estimated the proportion of oral and pharyngeal cancers in the United States that can be attributed to use of alcohol and cigarettes (population attributable risks). Among whites, 83% of the cases in men, 61% of the cases in women, and 73% of all cases were attributed to use of these substances. In blacks, these percentages were 90% for men, 68% for women, and 83% for both sexes. These are probably conservative estimates because individuals who consume less than one drink per week were included in the unexposed category, and some of these drinkers could have developed their disease as a result of their low level of exposure. The slightly higher population-attributable risk estimates for men than for women are due to greater exposure to alcohol and tobacco by men than by women, not to differences in the carcinogenic response to these substances by men and women (13). The higher population-attributable risks for blacks than for whites are due to both greater levels of exposure and to differences in relative risks of these cancers in the two racial groups (17). These findings have been replicated in Italy (8), where approximately 90% of the oral and pharyngeal cancers in males and 50% of those in females have been attributed to use of alcohol and tobacco. The obvious key to preventing these neoplasms is cessation of smoking and reduction of alcohol consumption.

## Laryngeal Cancers

As shown in Table 1, an elevated risk of laryngeal cancer in heavy users of alcohol was observed in eight cohort studies with external comparisons (1–3). A trend of increasing risk with amount of alcohol consumed was observed in a cohort study that used internal comparisons (4).

Results from 13 case–control studies were summarized by the IARC working group in 1988 (1). Since then, at least 8 additional studies (18–25) have been completed. All have shown an increase in risk of laryngeal cancer with amount of alcohol consumed after controlling for smoking. Results from 4 studies (20,22,26,27) that estimated risks separately for the extrinsic

**Table 2.** Relative risks of oral, pharyngeal, and other upper aerodigestive tract cancers in cohorts of heavy users of alcohol, internal comparisons.

| Neoplasm and study group | Reference group | High-risk group | Relative risk | 95% CI |
| --- | --- | --- | --- | --- |
| Oral cavity | | | | |
| Japanese adults[a] | Nondrinkers | Daily | 2.3 | NA |
| Pharynx | | | | |
| Japanese adults[a] | Nondrinkers | Daily | 2.4 | NA |
| Oral cavity, pharynx, esophagus | | | | |
| Kaiser-Permanente[b] | Nondrinkers | ≥6 drinks/day | 4.0 | 1.7–7.9 |
| Oral, pharynx, esophagus, larynx | | | | |
| Japanese doctors[b] | Occasional | ≥2 g/day | 8.6 | 6.9–10.6 |
| Hawaiian–Japanese[c] | Nondrinkers | ≥30 ml/day | 5.4 | 2.8–10.4 |

NA, not applicable. [a]Data from Hirayama (4). [b]Data from IARC (1). [c]Data from Kato et al. (5).

**Table 3.** Relative risks[a] of cancer of the extrinsic and intrinsic[b] larynx associated with varying levels of alcohol consumption.

| Reference, measure of alcohol | Amount of alcohol consumed | | | | |
|---|---|---|---|---|---|
| Elwood (26), ml/week | <1 | 1–4 | 5–9 | 10–19 | ≥20 |
| Extrinsic | 1.0 | 1.7 | 2.6 | 5.1 | 6.4 |
| Intrinsic | 1.0 | 1.1 | 0.7 | 2.0 | 2.2 |
| Guenel (22), g/day | 0–39 | 40–99 | 100–159 | ≥160 | |
| Extrinsic | 1.0 | 2.3 | 9.8 | 35.7 | |
| Intrinsic | 1.0 | 1.6 | 3.6 | 14.9 | |
| Tuyns (27), g/day | 0–40 | 41–80 | 81–120 | ≥121 | |
| Extrinsic | 1.0 | 2.2 | 4.6 | 10.2 | |
| Intrinsic | 1.0 | 1.1 | 1.8 | 2.7 | |
| Muscat (20), ml/day | <30 | 30–88 | 89–206 | ≥207 | |
| Extrinsic | 1.0 | 1.2 | 2.7 | 9.6 | |
| Intrinsic | 1.0 | 1.1 | 3.2 | 2.5 | |

[a]All relative risk estimates adjusted for smoking. [b]Definitions of extrinsic and intrinsic larynx vary among the studies (20,22,26,27).

and intrinsic larynx are summarized in Table 3. An increase in risk with amount of alcohol consumed is consistently observed for both cancers of the intrinsic and extrinsic larynx. However, the relative risks are consistently greater for cancers of the extrinsic larynx, suggesting a topical carcinogenic action for alcohol, since only the extrinsic larynx comes in direct contact with ingested materials. It should be noted that the definition of intrinsic and extrinsic larynx varies among the 4 studies shown in the table. This may partly explain the (relatively minor) differences in results among the studies.

Most studies that have assessed the joint effects of alcohol and tobacco use have found that the effects of these two exposures on the larynx are roughly multiplicative, providing evidence for biological synergism. Studies in France (27) have shown this approximate multiplicative joint effect for both the extrinsic and intrinsic larynx.

Associations between laryngeal cancer and alcohol have been reported for all types of alcoholic beverages. There have been no recent estimates of the proportion of laryngeal cancers in the United States that are likely attributable to alcohol or the joint effects of alcohol and tobacco. In 1980, Rothman (28) estimated that 50% of the cases in men and 40% of the cases in women were due to alcohol. More recently, it has been estimated that in Italy 82% of the cases in men and 84% of the cases in women are a result of exposure to both alcohol and tobacco (24). It is probably reasonable to assume that similar proportions of laryngeal cancer cases in the United States are attributable to alcohol and cigarette smoking.

## Esophageal Cancer

As shown in Table 1, in 9 of 10 cohort studies using external comparisons (1–3), an increase in risk of esophageal cancers was observed in alcoholics and other groups heavily exposed to alcohol. The one exception, the Dublin brewery workers, drank mainly beer and may not have been as heavily exposed to alcohol as individuals in most of the other study groups shown in the table. In one cohort study with internal comparisons (4), a trend of increasing risk with amount of alcohol consumed was observed.

The 1988 IARC working group (1) summarized results from 12 case–control studies. Since then, there have been at least 2 others in the United States (29,30), plus studies in Italy (12,31) and China (32). A trend of increasing risk of esophageal cancer with amount of alcohol consumed has consistently been observed after controlling for smoking.

Most studies have not distinguished adenocarcinomas from squamous cell carcinomas of the esophagus. In the United States, there has been an increase in incidence rates of adenocarcinomas of the esophagus since the mid-1970s (33). This increase has been particularly strong for white males. Most of the adenocarcinomas occur in the lower third of the esophagus. Many of these tumors occur in the gastroesophageal junction and appear to be similar in etiology to cancers of the gastric cardia. Therefore, in some studies, adenocarcinomas of the lower esophagus, gastroesophageal junction, and gastric cardia are combined for analytic purposes. Kabat et al. (30) found an increase in risk of both squamous cell esophageal cancers and gastroesophageal adenocarcinomas with increasing

amounts of alcohol consumed per week. However, the relative risk estimates were higher for squamous cell cancers than for adenocarcinomas. Similar findings have recently been observed in other studies in the United States (34) and China (32). Until recently, adenocarcinomas constituted a small proportion of all esophageal cancers, and results from studies that do not specifically distinguish between the two histologic types, summarized below, may be assumed to apply primarily to squamous cell carcinomas.

The joint effects of alcohol and smoking on risk of esophageal cancers appear to be more than additive and consistent with a multiplicative effect. There is, however, also clearly an association between risk of esophageal cancer and alcohol use in the absence of tobacco. This has been noted in France for both sexes (35) and in Italy for drinkers of wine, beer, and distilled spirits (31). In a study in France (36), the effect of alcohol appeared to be greater in individuals with a poor intake of fresh meat, citrus fruits, and oils than in individuals with adequate intake of these substances.

Studies in various parts of the world have shown associations between risk of esophageal cancer and all major types of alcoholic beverages. Some studies, however, have suggested that the effects are stronger for distillates than for beer or wine (29). Also, studies in various parts of the world have implicated homemade distillates as particularly strong risk factors for esophageal cancers. These include moonshine in the United States (29), samou in Singapore (1), cachaca in Brazil (1), and apple brandy in Normandy, France (1). These observations suggest that in addition to alcohol impurities in some homemade distillates may also contribute to the carcinogenic process.

The proportions of squamous cell esophageal cancers attributable to alcohol and tobacco use in the United States have recently been estimated to be 93% for blacks and 86% for whites (37). It must be emphasized, however, that the population-attributable risks for esophageal cancer with respect to alcohol vary markedly among different regions of the world. In some Eastern countries such as Iran, where alcohol use is proscribed, rates of esophageal cancer are very high, but the proportion of cases due to alcohol is very low. The estimates of the population-attributable risks for the United States are, therefore, not applicable to many other countries.

## Stomach Cancer

As shown in Table 4 (1–3), rates of stomach cancer generally are not increased in cohorts of individuals exposed to alcohol. These studies, however, do not distinguish cancers of the gastric cardia from more distal gastric carcinomas. Case–control studies of gastric carcinomas that have not distinguished neoplasms arising in different parts of the stomach have also tended not to show associations between alcohol use and stomach cancer. However, two case–control studies (38,39) have clearly shown an increase in risk of cancers of the gastric cardia, but not of cancers in other gastric subsites, with amount of alcohol consumed; and two others (40,41) found stronger associations between alcohol and cancers of the cardia than between alcohol and cancers elsewhere in the stomach. Studies in Japan (41), Sweden (42), and Poland (43) provide evidence to suggest that alcohol may potentiate an effect of cigarette smoke on risk of gastric cancer. In the Japanese and Polish studies, this potentiating effect appears to be particularly important in cancers of the gastric cardia. The latter study, however, may be suspect because, unlike most other studies, a strong association between cancers of the noncardia region of the stomach and vodka drinking was observed. These findings of an interactive effect between tobacco and alcohol for cancers of the gastric cardia require independent confirmation.

## Colon Cancer

Table 4 shows that there has been no consistent association observed between alcohol use and risk of colon cancer among multiple cohort studies (1–3) that used external comparisons. In a recent review of 15 case–control and cohort studies, Potter et al. (44) reported that in 7 of these studies a positive association of colon cancer with heavy alcohol use was observed. Most of the studies that assessed risk in relation to heavy use of alcohol found an increase in risk associated with such use, but most of the relative risk estimates were small and not significantly greater than one. Results from three recent studies (45–47) are similar to those cited by Potter et al. (44). On balance, the results from all epidemiologic studies, in the aggregate, do not suggest that alcohol is an important cause of colon cancer.

## Rectal Cancer

Table 4 shows that heavy users of alcohol have not consistently been observed to be at increased risk of cancers of the rectum. Of 21 general population studies summarized by Potter et al. (44), only 12 showed an association between alcohol use and rectal cancer. Positive but not significant trends of increasing risk of rectal cancer with increasing amounts of alcohol consumed daily were observed in two recent cohort studies (46,47).

A somewhat more consistent association has been observed between rectal cancer and consumption of beer than with consumption of other alcoholic beverages. The IARC working group (1) noted that five of eight case–control studies reported an association between beer intake and risk of rectal cancer in men. In most instances the studies contained too few females for meaningful analysis, but in three of six studies, a similar association was observed in women as in men. In a recent cohort study in the Netherlands (46), a significant trend of increasing risk with increasing beer consumption was observed. In the Iowa cohort study of women (47), a nonsignificant relative risk of 1.4 was observed in relation to beer consumption; an increase in risk of similar magnitude was also observed for consumption of liquor but not for wine. On balance, the results from epidemiologic studies of beer drinking and rectal cancer, although not totally consistent, do suggest the possibility of a true small increase in risk in relation to consumption of this particular beverage. If consumption of beer does increase risk of rectal cancer, the effect is a weak one. The possibility that it does, however, warrants further research efforts.

## Liver Cancer

As shown in Table 4, heavy users of alcohol have consistently been shown to be at increased risk of liver cancer in cohort studies that use external comparisons (1–3). The effect of alcohol on risk may, however, be overestimated in these studies because such studies fail to take into account the possible confounding effect of hepatitis B virus (HBV), which is a strong risk factor for hepatocellular carcinomas. On the other hand, some studies of this type may provide underestimates of the relative risk because some individuals in these studies may erroneously have been considered to have hepatocellular carcinoma when they in fact had metastatic liver cancers or other neoplasms of the hepatobiliary system.

There have been multiple case–control studies of liver cancer, but most of the earlier ones did not include measurements of hepatitis B virus antibodies and, therefore, are uninterpretable. Studies that did include measurement of HBV surface antigen have all shown an increase in risk of hepatocellular carcinoma in relation to this factor. Studies in the United States (48) and Spain (49) found increased risks associated with alcohol consumption after controlling for HBV status, although some earlier studies did not (1). In a case–control study within a Japanese cohort of HBV surface antigen-positive blood donors (50), an increased relative risk with amount of alcohol consumed was observed among HBV-positive individuals. The results among studies are thus inconsistent, but some suggest a causal relationship between hepatocellular carcinoma and alcohol consumption. The IARC working group (1) concluded in 1988 that there is a causal relationship between alcohol and liver cancer. This appears, however, to be a rare complication of alcohol use in the United States, since hepatocellular carcinomas are

**Table 4.** Relative risks of cancers of the stomach, colon, rectum, liver, and pancreas in cohorts of users of alcohol, external comparisons.[a]

| Study group | Stomach | Colon | Rectum | Liver | Pancreas |
|---|---|---|---|---|---|
| Norwegian alcoholics | 1.3 | 1.0 | 1.9 | 2.0 | 0.9–1.6[e] |
| Finnish alcohol misusers | | 1.0 | | 1.5[d] | |
| Finnish alcoholics | 0.8 | 1.8 | | 2.5 | 1.8 |
| Massachusetts alcoholics | 1.0 | 0.6 | 0.7 | 1.0 | 0.6 |
| U.K. alcoholics | 0.8 | 1.3 | 0.9 | 5.8[d] | 1.5 |
| Dublin brewery workers | 0.8 | 1.3 | 1.6[d] | 1.3 | 1.2–1.5[e] |
| U.S. veteran alcoholics | 1.0 | 0.8 | 3.3 | | 0.9 |
| Danish brewery workers | 0.9 | 1.1 | 1.0 | 1.5 | 1.1 |
| Canadian alcoholics | 1.0 | 1.0 | 1.0 | 2.0 | 0.8–1.2[e] |
| Swedish alcoholics[b] | 0.9 | 1.2 | 0.8 | 6.4[d] | 1.5 |
| Danish alcoholics[c] | 1.3 | 1.0 | 1.0 | 3.9[d] | 1.3[d] |
| Total (O/E) | 1.0 (322/311) | 1.0 (346/333) | 1.1 (213/198) | 1.9[d] (191/97.7) | 1.2 (161/129.9) |

[a]Data from IARC (1). [b]Data from Adami et al. (3). [c]Data from Tonnesen et al. (2). [d]Lower 95% confidence limit > 1.0. [e]Relative risk estimates varied depending on comparison group.

uncommon in this country. Results from one study in South Africa (1) suggest that the combined effects on risk of hepatocellular carcinoma of alcohol and HBV are additive. If so, then alcohol also would not be a major cause of hepatocellular carcinoma in HBV endemic areas. On the other hand, if alcohol potentiated the effect of HBV or vice versa, then alcohol consumption could be a major contributor to hepatocellular carcinoma in HBV endemic areas. The interactive effects of alcohol and HBV on risk of hepatocellular carcinoma are, therefore, worth further investigation.

## Pancreatic Cancer

As demonstrated in Table 4, results from cohort studies with external comparisons do not consistently show an increase in risk of pancreatic cancer in heavy users of alcohol. The summary of relative risk of 1.2 is not statistically significant, and the relative risk estimate from only one of the studies was significantly greater than unity. Furthermore, none of the five cohort studies with internal comparisons considered by the IARC working group (1) showed evidence of an association of pancreatic cancer with alcohol use. The IARC working group also summarized results from 14 case–control studies. The results of at least 5 more studies have been published (51–55). Of these 19 studies, only 4 provide evidence for a weak trend of increasing risk with increasing amounts of alcohol consumed. These trends generally were not statistically significant and were not always consistent among men and women. Five other studies found no trends in risk with level of exposure. Ten other studies did not report results by amount of alcohol consumed; the point estimates of the relative risks from these studies for individuals who were users of alcohol generally were close to unity and not statistically significant. On balance, there is currently little evidence for a causal association between alcohol use and risk of pancreatic cancer. However, cohort studies of alcoholics may not have been large enough to detect a modest elevation in risk of pancreatic cancer, and interviews of the relatives of subjects in case–control studies may have yielded underestimates of alcohol consumption. It is thus possible that very heavy alcohol drinking could be a risk factor for pancreatic cancer, and this should be evaluated in future studies.

### Breast Cancer

A careful review by Rosenberg et al. (56) of the possible relationship between alcohol

consumption and breast cancer was published in 1993. The authors sensibly included in their review only studies in which relative risk estimates were controlled for the potential confounding effects of various reproductive factors known to be associated with risk of breast cancer. Results from two additional population-based case–control studies (57,58) and one cohort study with internal comparisons (59) that meet these criteria have since been published. Five of 7 hospital-based case–control studies, 9 of 12 population-based case–control studies, and 8 of 9 cohort studies yielded relative risk estimates for breast cancer in heavy users of alcohol that were greater than unity. The relative risks ranged from 1.0 to 16.7 in the hospital-based case–control studies, from 0.5 to 1.9 in the population-based case–control studies, and from 0.8 to 3.3 in the cohort studies. Differences in reference groups and in definitions of heavy drinking among studies preclude a direct comparison of relative estimates, but there are no systematic differences in results by type of investigation to suggest bias related to study design. Also results are not consistently different between studies that did and did not adjust also for dietary factors or for body mass index.

In 1991, Howe (60) published results of a metaanalysis of data from six case–control studies that were chosen because information was available on caloric intake and consumption of specific nutrients. Overall, the relative risk in individuals who ever drank alcoholic beverages was estimated to be 1.0. However, the relative risk tended to increase with daily alcohol consumption greater than 40 g of alcohol (about three drinks per day). The increase in risk at this level of intake was noted in all four studies that provided information on users of this amount of alcohol. The authors concluded that there is a threshold below which risk of alcohol is not altered. More recently, Longnecker et al. (61) evaluated data from 38 epidemiologic studies. A strong trend of increasing risk with increasing numbers of drinks per day was observed in data from these investigations. The authors were appropriately cautious in concluding that a role for alcohol in the genesis of breast cancer has not been firmly established. However, the general consistency of the results of most studies and the results of this metaanalysis suggest that there may well be a weak causal relationship between alcohol and risk of breast cancer. This conclusion is, however, disputed by the authors of another recent review (62). Further studies

of this issue clearly are warranted. A randomized study with a crossover design (63) showed that when women were given 30 mg of alcohol per day for three menstrual cycles, this resulted in significant increases in levels of both serum and urinary estrogens. This could provide a biological mechanism for the observed associations of breast cancer risk with alcohol consumption and warrants replication.

### Other Cancers

No significant associations have been reported between alcohol consumption and cancers of the lung, bladder, ovary, prostate, testis, brain, thyroid, or kidney, or for leukemias or lymphomas (1).

### Mechanisms of Action

In an excellent review of the issue of alcohol and cancer, Blot (64) summarized the possible mechanisms by which alcohol could increase the risks of various neoplasms. Alcoholic beverages may be contaminated with known carcinogens. As indicated above, the evidence for this is strongest for the relationship between alcohol and esophageal carcinoma. N-Nitroso compounds, which are precursors of nitrosamines, are found in some types of beer; micotoxins have been found in some wines and in beer in South Africa; urethane has been identified in fruit brandies in France; tannins are found in some wines; and inorganic arsenic and asbestos have been isolated from other alcoholic beverages.

Acetaldehyde, a metabolite of ethanol, has been shown to be carcinogenic in some animal systems. This could result in a systemic carcinogenic effect and influence the development of cancer at sites other than where alcohol is absorbed. This might include cancers of the colon, pancreas, and breast.

Alcohol can act as a solvent to enhance the absorption of other carcinogens. This would imply a topical effect of alcohol and provide a mechanism for the possible interaction between alcohol and tobacco. This mechanism might be involved in the development of cancers of the mouth, oral pharynx, and extrinsic larynx.

Individuals who consume large amounts of alcohol frequently substitute alcohol for other foods as a source of calories. Such individuals may therefore be deficient in nutrients that are not present in alcohol. These could include many of the micronutrients that have been associated with a reduced risk of a number of different neoplasms.

Chronic use of alcohol can lead to liver cirrhosis and a compromised liver function. This, in turn, can reduce the absorption of nutrients and their delivery to target cells. Compromised liver function can also inhibit detoxification of carcinogenic compounds that are ingested. The effect of alcohol on nutritional status and liver function may also suppress immune function.

Alcohol may also induce the activity of enzymes that can convert some compounds to carcinogens (e.g., tobacco-specific nitrosamines). This might also be a mechanism for the interaction of tobacco and alcohol in the genesis of cancers of the upper aerodigestive tract.

## Discussion and Summary

A causal relationship probably exists between alcohol and cancers of the mouth and oral pharynx, larynx, and esophagus. If, based on estimates by others (17,24,28,37) of the proportions of these cancers that are attributable to use of tobacco and alcohol, we assume that 75% of the oral, pharyngeal, and laryngeal cancers, and 85% of the esophageal cancers in the United States are a direct consequence of smoking and drinking, then this would account for 3.4% of all cancers that occur in this country annually (65). This would represent about 41,000 new cancer cases and approximately 18,000 deaths in 1994 (65). The number of these cancers due only to alcohol cannot be confidently estimated because of insufficient data on risk in relation to alcohol in the absence of tobacco as well as to uncertainty about the quantitative nature of the interactive effects of these two substances on risks.

Alcohol is a likely contributor to the burden of liver cancer in the United States, although this is less well established than for upper aerodigestive tract cancers. If alcohol does cause liver cancer, then these neoplasms are relatively rare consequences of excess alcohol consumption in the absence of HBV. There is insufficient information regarding the possible interaction between alcohol and HBV. If such an interaction were to occur, then alcohol could have a major impact on the occurrence of liver cancer in HBV-endemic areas.

A possible causal relationship may also exist between alcohol and breast cancer and this possibility warrants high priority for additional research. Alcohol probably does not appreciably contribute to the development of cancers of the colon or pancreas, although a possible increase in risk of pancreatic carcinomas in heavy drinkers warrants further study. There is weak and inconsistent evidence that alcohol consumption, particularly beer drinking, increases the risk of cancers of the rectum. This possibility, however, also warrants further investigation.

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